JOURNAL OF VIROLOGY, Jan. 1997, p. 839–842 Vol. 71, No. 1
0022-538X/97/$04.00+0

Human Herpesvirus 8 Encodes a Homolog of Interleukin-6

FRANK NEIPEL,[1]* JENS-CHRISTIAN ALBRECHT,[1] ARMIN ENSSER,[1] YAO-QI HUANG,[2] JIAN JUN LI,[2] ALVIN E. FRIEDMAN-KIEN,[2] AND BERNHARD FLECKENSTEIN[1]

Institut für Klinische und Molekulare Virologie, Universität Erlangen-Nürnberg, D-91054 Erlangen, Germany,[1] and Departments of Microbiology and Dermatology, New York University Medical Center, New York, New York 10016[2]

Received 17 September 1996/Accepted 8 October 1996

Kaposi's sarcoma is a multifocal lesion that is reported to be greatly influenced by cytokines such as interleukin-6 (IL-6) and oncostatin M. DNA sequences of a novel human gammaherpesvirus, termed human herpesvirus 8 (HHV-8) or Kaposi sarcoma-associated herpesvirus, have been identified in all epidemiological forms of Kaposi's sarcoma with high frequency. The presence of HHV-8 DNA is also clearly associated with certain B-cell lymphomas (body cavity-based lymphomas) and multicentric Castleman's disease. Sequence analysis of a 17-kb fragment revealed that adjacent to a block of conserved herpesvirus genes (major DNA-binding protein, glycoprotein B, and DNA polymerase), the genome of HHV-8 encodes structural homolog of IL-6. This cytokine is involved not only in the pathogenesis of Kaposi's sarcoma but also in certain B-cell lymphomas and multicentric Castleman's disease. The viral counterpart of IL-6 (vIL-6) has conserved important features such as cysteine residues involved in disulfide bridging or an amino-terminal signal peptide. Most notably, the region known to be involved in receptor binding is highly conserved in vIL-6. This conservation of essential features and the remarkable overlap between diseases associated with HHV-8 and diseases associated with IL-6 disregulation clearly suggest that vIL-6 is involved in HHV-8 pathogenesis.

Kaposi's sarcoma (KS), a multifocal proliferative lesion of uncertain pathogenesis, is highly prevalent among homosexual AIDS patients. The originally described form (classical KS) occurs sporadically in some populations in eastern and southern Europe. KS is frequently found in central Africa, where the tumor occurs in young patients. The particular epidemiology among AIDS patients had suggested that an infectious agent other than human immunodeficiency virus is involved in KS pathogenesis. Studies with biopsy materials and cultured cells have indicated an important role for growth factors and cellular cytokines, such as basic fibroblast growth factor (35), interleukin-1β (IL-1β) (22), IL-6 (6, 19, 23, 25, 26, 33, 38), and oncostatin M (5, 7, 29, 32), for the proliferation of spindle cells in KS (24). Chang and colleagues (8) stirred considerable interest when they detected DNA sequences of a novel herpesvirus in KS tissues of AIDS patients. Meanwhile, DNA of this virus was consistently found in all epidemiological forms of KS (9, 11, 12, 18, 27, 31). The new virus, termed human herpesvirus 8 (HHV-8), shows marked sequence homology to herpesvirus saimiri, the prototype of gamma-2 herpesvirus; thus, HHV-8 appears to be the first human member of the gamma-2 herpesviruses (genus *Rhadinovirus*). Sequencing of a HHV-8 DNA fragment with a size of 20.7 kb indicated a genome organization that is collinear to herpesvirus saimiri, at least within an area of 17 open reading frames (ORFs) (28), which has been confirmed by sequence analysis of a further 50 kb (29a). Rhadinovirus genomes consist of a unique L-DNA that codes for 72 proteins (herpesvirus ateles) (1a) to 85 proteins (alcelaphine herpesvirus 1) (14a). The L-DNA is flanked by multirepetitive DNA that is high in GC content (H-DNA). Most strikingly, rhadinovirus genomes contain a surprisingly high number of genes that have apparently been acquired from the host cell. They include the genes coding for enzymes involved in the nucleotide metabolism (thymidilate synthetase [17] and dihydrofolate reductase [DHFR] [36]) and complement-controlling proteins (CCPH [1] and CD59 [3]) and genes that could be involved in proliferation control, such as those encoding cyclins (20), the cytokine IL-17, and the IL-8 receptor (2). In the course of structural studies of the HHV-8 genome, we have now found a gene that encodes a structural equivalent of IL-6, providing the first known example of an IL-6-type gene in a viral genome.

DNA was extracted from a KS biopsy specimen, partially digested with the restriction endonuclease *Sau*3A (0.2 U/μg of DNA for 2 min), and enzymatically ligated with *Bam*HI-digested arms of the bacteriophage lambda DASHII (Stratagene, Inc., La Jolla, Calif.). Initially, this genomic library from KS tissue was screened with probes constructed according to the HHV-8 sequence information published by Chang and colleagues (8). HHV-8-positive lambda clones isolated by this method were sequenced using a shotgun approach (34), and terminal fragments were used as probes for further screening of the genomic library from KS tissue. Using the BLAST algorithm for amino acid comparisons (4), we found an ORF with significant homology to IL-6 (Fig. 1). The ORF for the viral homolog to IL-6 (vIL-6) has the coding capacity for a polypeptide of 204 amino acids (Fig. 2). It is located adjacent to a region with collinearity to the glycoprotein B/DNA polymerase block of herpesvirus saimiri. The reading frame to the left of vIL-6 is homologous to ORF11 of herpesvirus saimiri. Although vIL-6 is the positional analog of herpesvirus saimiri ORF12, these two genes are not homologous on the DNA or protein level. The HHV-8 reading frame to the left of vIL-6 encodes a gene with extensive homology to mammalian DHFR genes (29a), a gene that is also present in herpesvirus saimiri (Fig. 1). Interestingly, the DHFR gene of herpesvirus saimiri has a different genomic position: it is located close to the left end of the genome (ORF2). ORF13 of herpesvirus saimiri, which would be the positional analog of HHV-8 DHFR, encodes an unrelated protein with homology to IL-17. vIL-6 is

* Corresponding author. Mailing address: Institut für Klinische und Molekulare Virologie, Universität Erlangen-Nürnberg, Schlossgarten 4, D-91054 Erlangen, Germany. Phone: 49-9131-856583. Fax: 49-9131-856599. E-mail: neipel@viro.med.uni-erlangen.de.

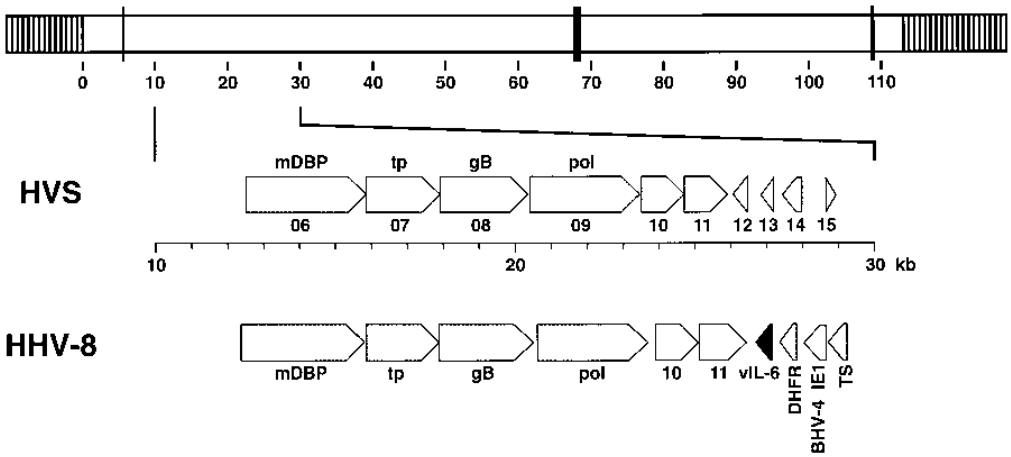

FIG. 1. Genomic position of glycoprotein B/DNA polymerase block of HHV-8 relative to the herpesvirus saimiri genome. The top part is a schematic drawing of the herpesvirus saimiri genome, with vertical bars representing areas of repetitive sequence. The glycoprotein B (gB)/DNA polymerase (pol) gene block is drawn below on a larger scale. ORFs and their orientations are indicated by large arrows. Genes for which homologs could be identified in HHV-8 and herpesvirus saimiri (HVS) are shaded, and genes without known homologs are symbolized by open arrowheads. The ORF for vIL-6 is shown as a closed arrowhead. This area contains four genes that are found in all herpesviruses sequenced so far: the major DNA-binding protein (mdbp), a putative transport/capsid assembly protein (tp), glycoprotein B, and the DNA polymerase. The ORFs labeled 10 and 11 also share homology with their counterparts in herpesvirus saimiri. vIL-6 is located immediately adjacent to genes 10 and 11 and is the first ORF within a divergent area of the HHV-8 genome. On the right of vIL-6 are reading frames with homology to DHFR, the bovine herpesvirus 4 immediate-early gene 1 (BHV-4 IE1), and thymidylate synthetase (TS) (29a). There is no homology to bovine herpesvirus 4 immediate-early gene 1 in herpesvirus saimiri. Reading frames encoding homologs of DHFR and thymidylate synthase are present in the herpesvirus saimiri genome, although at different genomic positions (ORF2, DHFR; ORF70, thymidylate synthase) (3).

24.74% identical to human IL-6 (similarity, 49.73%), 24.23% identical to murine IL-6 (similarity, 47.94%), 25.97% identical to porcine IL-6 (similarity, 52.91%), and 24.60% identical to bovine IL-6 (similarity, 49.73%) in amino acid sequence alignments calculated for the complete vIL-6 protein with the program GAP (Genetics Computer Group, Madison, Wis.). Most notably, in the viral gene product all four cysteine residues that are known to be involved in disulfide bridging are conserved, and the gene product shows a characteristic signal peptide of 22 amino acids (Fig. 2). The amino acid sequence homology of vIL-6 to the human IL-6 precursor is especially pronounced between amino acids 98 and 123 of the human sequence (Fig. 2 and 3). This area is known to be involved in binding to the IL-6 receptor (13, 14, 37). The domains required for IL-6 signal transduction are not well established. Based on the sequence similarity, binding of vIL-6 to the IL-6 receptor appears to be likely. However, it is also possible that by binding to the receptor, vIL-6 blocks signal transduction or alters receptor turnover. It may also not act on all the cell types that respond to cellular IL-6.

In general, genes sequestered from their host cell by herpesviruses have been shown to be functional. For example, ORF13 of herpesvirus saimiri encodes a homolog of IL-17 (vIL-17) that, like its cellular counterpart, stimulates the secretion of IL-6, IL-8, granulocyte colony-stimulating factor, and prostaglandin E2 (15). A homolog of IL-17 has not been identified in HHV-8 so far. HHV-8 encodes vIL-6 instead at a genomic position which is similar to the position of ORF13 in herpesvirus saimiri. Thus, vIL-6, which is structurally unrelated to IL-17, could provide some of the functions of vIL-17. This possibility supports, in addition, the notion that vIL-6 is a functional cytokine.

The pathogenesis of KS is still an enigma. It is generally accepted that dysregulated cytokine production is an important factor for the development of KS. It is also generally accepted that an infectious agent other than human immunodeficiency virus is responsible for the high prevalence of KS among certain groups of AIDS patients. There is still considerable controversy about the cytokine(s) most important for continuous growth of cultured KS spindle cells. Oncostatin M and IL-6 have been suspected to be involved in KS pathogenesis by several groups of investigators. Both proteins belong to the same family of cytokines, and in part, they share receptor and signaling pathways. Although some groups have reported that cultured KS cells respond to human recombinant IL-6 with increased growth, this has not been confirmed by others. A possible role of IL-6 for KS pathogenesis is supported by the finding that KS spindle cells express the high-affinity IL-6 receptor in vivo (26). The hypothesis that HHV-8 may be the

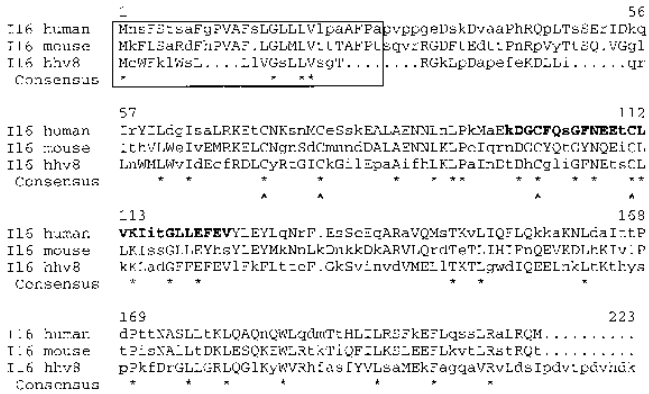

FIG. 2. Sequence alignment of predicted precursor of HHV-8 vIL-6 gene with those of human and mouse IL-6. Amino acids identical in all three proteins are indicated by asterisks, and cysteine residues involved in disulfide bridging are marked with carets. Uppercase letters symbolize amino acids conserved according to the criteria defined by Dayhoff et al. (10). The first 28 amino acids of human and murine IL-6 are known to comprise a signal peptide which is cleaved posttranslationally. A signal peptide of 22 amino acids is predicted for vIL-6 by the program Signalp (30). Boldface letters indicate the region (amino acids 98 to 126 of the human IL-6-precursor) that is known to be involved in receptor binding. Amino acid identity of human IL-6 to the corresponding region of vIL-6 is 53%.

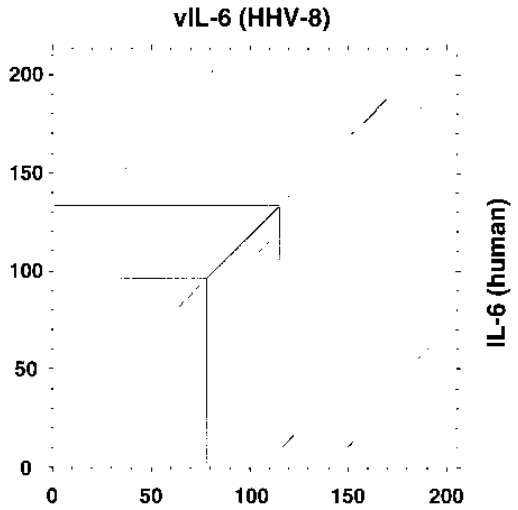

FIG. 3. Dot plot comparison of HHV-8 IL-6 (*x* axis) and human IL-6 (*y* axis). The dot plot comparison was calculated using the Genetics Computer Group suite of sequence analysis programs with the parameters for window and stringency set to 20 and 16, respectively. The well-conserved area, which is marked with continuous lines, is identical to the receptor-binding region of human IL-6 as identified by Ehlers et al. (13).

missing infectious agent was initially based on the detection of viral DNA only. HHV-8 DNA has been found in all epidemiological forms of KS in nearly 100% of cases, whereas DNA of this novel virus is infrequently seen in other tissue specimens and non-KS patients (9, 12, 18, 27). This finding is now supported for the first time by serological studies which show that HHV-8 occurs less frequently than most other human herpesviruses in the general population. However, the seroprevalence is high in groups at risk for the development of KS (16, 21). Detection of an IL-6 homolog in HHV-8 is highly suggestive that the respective viral gene product plays a functional role in the proliferation of typical KS cells. Two other disease conditions, Castleman's disease and body cavity-based lymphomas, have been found to be associated with the presence of HHV-8 DNA. A rare form of B-cell lymphoma in AIDS patients, body cavity-based lymphoma, invariably carries HHV-8 genomes in a latent state. Multicentric Castleman's disease is a chronic disease with benign hyperplastic lymphadenopathy. It is characterized by large lymph follicles with intervening plasma cells. The patients show marked hypergammaglobulinemia, and the B cells in such hyperplastic lymph nodes were found to produce large amounts of IL-6 by functional assays. Interestingly, in some patients, Castleman's disease may progress to multiple myeloma. Clinical improvement was associated with a decrease in serum IL-6 levels. Further studies are required to show whether functional assays are able to discriminate between cellular IL-6 and vIL-6. Based on DNA diagnostics, HHV-8 appears to be linked to three proliferative diseases, KS, body cavity-based B-cell lymphoma, and multicentric Castleman's disease, and a pathological role has been proposed for IL-6 in these diseases in the past, prior to the discovery of HHV-8. The identification of an IL-6 gene in HHV-8 thus supports the assumption that HHV-8 has a pathological role in these diseases and provides the basis for further investigation of its role in stimulating abnormal cellular proliferation.

Nucleotide sequence accession number. The vIL-6 sequence was submitted to GenBank and received accession number U73655.

This work was supported by Deutsche Krebshilfe, founded by Mildred Scheel, grant no. W134/94/F12.

REFERENCES

1. **Albrecht, J. C., and B. Fleckenstein.** 1992. New member of the multigene family of complement control proteins in herpesvirus saimiri. J. Virol. **66:** 3937–3940.
1a. **Albrecht, J. C., and B. Fleckenstein.** Unpublished data.
2. **Albrecht, J.-C., J. Nicholas, D. Biller, K. R. Cameron, B. Biesinger, C. Newman, S. Wittmann, M. A. Craxton, H. Coleman, B. Fleckenstein, and R. W. Honess.** 1992. Primary structure of the herpesvirus saimiri genome. J. Virol. **66:**5047–5058.
3. **Albrecht, J. C., J. Nicholas, K. R. Cameron, C. Newman, B. Fleckenstein, and R. W. Honess.** 1992. Herpesvirus saimiri has a gene specifying a homologue of the cellular membrane glycoprotein CD59. Virology **190:**527–530.
4. **Altschul, S. F., W. Gish, W. Miller, E. W. Myers, and D. J. Lipman.** 1990. Basic local alignment search tool. J. Mol. Biol. **215:**403–410.
5. **Amaral, M. C., S. Miles, G. Kumar, and A. E. Nel.** 1993. Oncostatin-M stimulates tyrosine protein phosphorylation in parallel with the activation of p42MAPK/ERK-2 in Kaposi's cells. Evidence that this pathway is important in Kaposi cell growth. J. Clin. Invest. **92:**848–857.
6. **Bailer, R. T., A. Lazo, C. L. Ng Bautista, B. L. Hout, G. M. Ness, A. K. Hegtvedt, J. R. Blakeslee, R. E. Stephens, G. P. Brierley, and S. R. Mallery.** 1995. Comparison of constitutive cytokine release in high and low histologic grade AIDS-related Kaposi's sarcoma cell strains and in sera from HIV+/KS+ and HIV+/KS− patients. J. Interferon Cytokine Res. **15:**473–483.
7. **Cai, J., P. S. Gill, R. Masood, P. Chandrasoma, B. Jung, R. E. Law, and S. F. Radka.** 1994. Oncostatin-M is an autocrine growth factor in Kaposi's sarcoma. Am. J. Pathol. **145:**75–79.
8. **Chang, Y., E. Cesarman, M. S. Pessin, F. Lee, J. Culpepper, D. M. Knowles, and P. S. Moore.** 1994. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science **266:**1865–1869.
9. **Chang, Y., J. Ziegler, H. Wabinga, E. Katangole Mbidde, C. Boshoff, T. Schulz, D. Whitby, D. Maddalena, H. W. Jaffe, R. A. Weiss, and P. S. Moore.** 1996. Kaposi's sarcoma-associated herpesvirus and Kaposi's sarcoma in Africa. Uganda Kaposi's Sarcoma Study Group. Arch. Intern. Med. **156:**202–204.
10. **Dayhoff, M. O., R. M. Schwartz, and B. C. Ortcutt.** 1978. Atlas of protein sequence & structure, vol. 5, suppl. p345. National Biomedical, Washington, D.C.
11. **de Lellis, L., M. Fabris, E. Cassai, A. Corallini, G. Giraldo, C. Feo, and P. Monini.** 1995. Herpesvirus-like DNA sequences in non-AIDS Kaposi's sarcoma. J. Infect. Dis. **172:**1605–1607.
12. **Dupin, N., M. Grandadam, V. Calvez, I. Gorin, J. T. Aubin, S. Havard, F. Lamy, M. Leibowitch, J. M. Huraux, J. P. Escande, et al.** 1995. Herpesvirus-like DNA sequences in patients with Mediterranean Kaposi's sarcoma. Lancet **345:**761–762.
13. **Ehlers, M., J. Grotzinger, F. D. de Hon, J. Mullberg, J. P. Brakenhoff, A. Wollmer, and S. Rose John.** 1995. Residues 77–95 of the human interleukin-6 protein are responsible for receptor binding and residues 41–56 for signal transduction. Ann. N. Y. Acad. Sci. **762:**400–402.
14. **Ekida, T., C. Nishimura, S. Masuda, S. Itoh, I. Shimada, and Y. Arata.** 1992. A receptor-binding peptide from human interleukin-6: isolation and a proton nuclear magnetic resonance study. Biochem. Biophys. Res. Commun. **189:**211–220.
14a. **Ensser, A., R. Pflanz, and B. Fleckenstein.** Unpublished data.
15. **Fossiez, F., O. Djossou, P. Chomarat, L. Flores-Romo, S. Ait-Yahia, C. Maat, J.-J. Pin, P. Garrone, E. Garcia, S. Saeland, D. Blanchard, C. Gaillard, B. D. Mahapatra, E. Rouvier, P. Golstein, J. Bancherau, and S. Lebecque.** 1996. T cell interleukin-17 induces stromal cells to produce proinflammatory and hematopoietic cytokines. J. Exp. Med. **183:**2593–2603.
16. **Gao, S. J., L. Kingsley, M. Li, W. Zheng, C. Parravicini, J. Ziegler, R. Newton, C. R. Rinaldo, A. Saah, J. Phair, R. Detels, Y. Chang, and P. S. Moore.** 1996. KSHV antibodies among Americans, Italians and Ugandans with and without Kaposi's sarcoma. Nature Med. **2:**925–928.
17. **Honess, R. W., M. A. Craxton, L. Williams, and U. A. Gompels.** 1989. A comparative analysis of the sequence of the thymidine kinase gene of a gammaherpesvirus, herpesvirus saimiri. J. Gen. Virol. **70:**3003–3013.
18. **Huang, Y. Q., J. J. Li, M. H. Kaplan, B. Poiesz, E. Katabira, W. C. Zhang, D. Feiner, and A. E. Friedman Kien.** 1995. Human herpesvirus-like nucleic acid in various forms of Kaposi's sarcoma. Lancet **345:**759–761.
19. **Huang, Y. Q., J. J. Li, K. S. Kim, A. Nicolaides, W. G. Zhang, J. Le, B. J. Poiesz, and A. E. Friedman Kien.** 1993. HIV-1 infection and modulation of cytokine and growth factor expression in Kaposi's sarcoma-derived cells in vitro. AIDS **7:**317–322.
20. **Jung, J. U., M. Stager, and R. C. Desrosiers.** 1994. Virus-encoded cyclin. Mol. Cell. Biol. **14:**7235–7244.
21. **Kedes, D., E. Operalski, M. Busch, R. Kohn, J. Flood, and D. E. Ganem.** 1996. The seroepidemiology of human herpesvirus 8 (Kaposi's sarcoma-associated herpesvirus): distribution of infection in KS risk groups and evidence for sexual transmission. Nature Med. **2:**918–924.
22. **Louie, S., J. Cai, R. Law, G. Lin, Y. Lunardi Iskandar, B. Jung, R. Masood,**

and P. Gill. 1995. Effects of interleukin-1 and interleukin-1 receptor antagonist in AIDS-Kaposi's sarcoma. J. Acquired Immune Defic. Syndr. **8:**455–460.
23. **Masood, R., Y. Lunardi Iskandar, L. F. Jean, J. R. Murphy, C. Waters, R. C. Gallo, and P. Gill.** 1994. Inhibition of AIDS-associated Kaposi's sarcoma cell growth by DAB389-interleukin 6. AIDS Res. Hum. Retroviruses **10:**969–975.
24. **Miles, S. A.** 1992. Pathogenesis of human immunodeficiency virus-related Kaposi's sarcoma. Curr. Opin. Oncol. **4:**875–882.
25. **Miles, S. A., O. Martinez Maza, A. Rezai, L. Magpantay, T. Kishimoto, S. Nakamura, S. F. Radka, and P. S. Linsley.** 1992. Oncostatin M as a potent mitogen for AIDS-Kaposi's sarcoma-derived cells. Science **255:**1432–1434.
26. **Miles, S. A., A. R. Rezai, J. F. Salazar Gonzalez, M. Vander Meyden, R. H. Stevens, D. M. Logan, R. T. Mitsuyasu, T. Taga, T. Hirano, T. Kishimoto, et al.** 1990. AIDS Kaposi sarcoma-derived cells produce and respond to interleukin 6. Proc. Natl. Acad. Sci. USA **87:**4068–4072.
27. **Moore, P. S., and Y. Chang.** 1995. Detection of herpesvirus-like DNA sequences in Kaposi's sarcoma in patients with and without HIV infection. N. Engl. J. Med. **332:**1181–1185.
28. **Moore, P. S., S. J. Gao, G. Dominguez, E. Cesarman, O. Lungu, D. M. Knowles, R. Garber, P. E. Pellett, D. J. McGeoch, and Y. Chang.** 1996. Primary characterization of a herpesvirus agent associated with Kaposi's sarcoma. J. Virol. **70:**549–558.
29. **Murakami-Mori, K., T. Taga, T. Kishimoto, and S. Nakamura.** 1995. AIDS-associated Kaposi's sarcoma (KS) cells express oncostatin M (OM)-specific receptor but not leukemia inhibitory factor/OM receptor or interleukin-6 receptor. Complete block of OM-induced KS cell growth and OM binding by anti-gp130 antibodies. J. Clin. Invest. **96:**1319–1327.
29a. **Neipel, F., J.-C. Albrecht, A. Ensser, Y. Q. Huang, J. J. Li, A. E. Friedman-Kien, and B. Fleckenstein.** Unpublished data.
30. **Nielsen, H., J. Engelbrecht, S. Brunak, and G. von Heijne.** Identification of prokaryotic and eukaryotic signal peptides and prediction of their cleavage sites. Protein Eng., in press.
31. **Noel, J. C., P. Hermans, J. Andre, I. Fayt, T. Simonart, A. Verhest, J. Haot, and A. Burny.** 1996. Herpesvirus-like DNA sequences and Kaposi's sarcoma: relationship with epidemiology, clinical spectrum, and histologic features. Cancer **77:**2132–2136.
32. **Radka, S. F., S. Nakamura, S. Sakurada, and S. Z. Salahuddin.** 1993. Correlation of oncostatin M secretion by human retrovirus-infected cells with potent growth stimulation of cultured spindle cells from AIDS-Kaposi's sarcoma. J. Immunol. **150:**5195–5201.
33. **Scala, G., M. R. Ruocco, C. Ambrosino, M. Mallardo, V. Giordano, F. Baldassarre, E. Dragonetti, I. Quinto, and S. Venuta.** 1994. The expression of the interleukin 6 gene is induced by the human immunodeficiency virus 1 TAT protein. J. Exp. Med. **179:**961–971.
34. **Staden, R.** 1990. Finding protein coding regions in genomic sequences. Methods Enzymol. **183:**163–180.
35. **Stürzl, M., H. Brandstetter, C. Zietz, B. Eisenburg, G. Raivich, D. P. Gearing, N. H. Brockmeyer, and P. H. Hofschneider.** 1995. Identification of interleukin-1 and platelet-derived growth factor-B as major mitogens for the spindle cells of Kaposi's sarcoma: a combined in vitro and in vivo analysis. Oncogene **10:**2007–2016.
36. **Trimble, J. J., S. C. Murthy, A. Bakker, R. Grassmann, and R. C. Desrosiers.** 1988. A gene for dihydrofolate reductase in a herpesvirus. Science **239:**1145–1147.
37. **van Dam, M., J. Mullberg, H. Schooltink, T. Stoyan, J. P. Brakenhoff, L. Graeve, P. C. Heinrich, and S. Rose John.** 1993. Structure-function analysis of interleukin-6 utilizing human/murine chimeric molecules. Involvement of two separate domains in receptor binding. J. Biol. Chem. **268:**15285–15290.
38. **Yang, J., M. K. Hagan, and M. K. Offermann.** 1994. Induction of IL-6 gene expression in Kaposi's sarcoma cells. J. Immunol. **152:**943–955.